Global Regulatory Policy

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MERCK
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January 28, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket 04D-0493 - Guidance for Industry, Recommended Approaches to Integration of Genetic Toxicology Study Results

Merck & Co., Inc. is a leading worldwide human health product company. Merck's corporate strategy — to discover new medicines through breakthrough research — encourages us to spend nearly $3 billion annually on worldwide Research and Development (R&D). Through a combination of the best science and state-of-the-art medicine, Merck's R&D pipeline has produced many of the important pharmaceutical and biological products on the market today.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R&D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. In the course of developing products to treat and prevent a variety of diseases, Merck scientists regularly address issues affected by the draft guidance (hereafter referred to as the Guidance). Therefore, we are well qualified to comment on this guidance.

General Comments

Merck is pleased to have the opportunity to comment on the proposed Guidance on how to proceed with clinical studies while ensuring the safety of study participants, when results in genotoxicity studies are positive. We note that in general the proposed approaches are consistent with the ICH genotoxicity guidances S2A and S2B. We agree with the recommendation to use weight of evidence and information on mechanism or mode of action in determining whether genotoxicity data indicate any potential for risk to people. We applaud the overall concept that a sponsor may choose from several options to provide suitable evidence for evaluation, and we appreciate the statements in the proposed Guidance that allow flexibility, leaving open alternative approaches and emphasizing that the guidance comprises suggestions and recommendations, rather than requirements.

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We also welcome the clear statements on the circumstances that are appropriate for single-dose trials or multiple-dose clinical trials in normal volunteers when there are positive genotoxicity findings.

Completion of the Fourth Test in ICH Standard Battery

However, we strongly recommend that the proposed guidance be modified such that completion of the fourth test in the ICH standard battery is an option, and not a required first step in follow-up of a positive genetox test result. Lines 84-86 of the Guidance state, *If any of the three assays in the ICH genotoxicity standard battery is positive, then we recommend completing the fourth test in the ICH battery.* While the draft guidance overall is consistent with ICH S2A and S2B, the requirement to complete the fourth test does not appear consistent with the ICH guidances.

The completion of the fourth test should not be required, but rather be included in options A-C (Lines 89-160). This choice should be driven by the nature of the positive results in the ICH standard battery. There may be more relevant follow-up tests that contribute more to weight of evidence (WOE) or mechanism of action (MOA) assessments. The most common scenario would be following a positive result in either the mouse lymphoma cell mutation assay or the *in vitro* chromosome aberration assay. Both the aberration assay and the mouse lymphoma cell mutation assay are known to be prone to false or irrelevant positive results, and since mechanisms that can lead to indirect or irrelevant positive results operate in both assays, doing both tests is not the best way to add information useful in assessing potential risk. As a general principle, a follow-up assay should be one that elucidates mechanism or adds understanding, and should not be an assay prone to false positive results. Completion of the fourth test might be most suitably included under option A, in Weight of Evidence.

Other Comments

Additional comments appear in the order that the topics appear in the Guidance and are referenced by line number.

Lines 37-41: The Guidance states, *For the purpose of this guidance, a single-dose clinical study is defined as a study involving a single administration or up to 24 hours of an intravenous infusion of a drug product. Repeat-dose studies are studies involving multiple administrations or infusions of more than 24 hours duration.* ***Administration of sustained-release preparations or agents with an in vivo half-life of greater than 12 hours can result in systemic exposure for greater than 24 hours.***
Merck Comment: It should be noted that drugs administered once in standard formulations can have half-lives greater than 12 hours. We recommend that the FDA include as part of the definition of single-dose studies cases of sustained release preparations with systemic exposure not greatly exceeding 24 hours. Further, we request

that the Agency clarify the intent of inclusion of the bolded statement or omit the bolded sentence altogether.

Lines 47-48: The Guidance states, *Risk for carcinogenesis is usually determined in rodent assays, either 2-year studies or shorter-term studies using alternative models.*[3] *(ICH S1B)*
Merck Comment: We concur that risk for carcinogenesis is usually determined in rodent assays *in vivo* (either 2-year or short term alternative models) with reference to ICH S1B. However, this Guidance should clarify that the assays referred to in ICH S1B are *in vivo* models only and do not include *in vitro* models such as the SHE cell transformation assay.

Lines 65-66: The Guidance states, *Pharmaceuticals that give positive results in genetic toxicology assays but do not directly interact with DNA do not always present a significant in vivo risk.*
Merck Comment: We agree with this statement. However, the Agency may wish to consider a potential source of ambiguity in this sentence. Readers may think that "direct" in the context of genotoxicity means acting without metabolic activation. Therefore, the sentence may read more clearly if modified to state, *Pharmaceuticals that give positive results in genetic toxicology assays but do not react with DNA with or without metabolic activation do not always present a significant in vivo risk.*

Lines 81-82: The Guidance states, *In general, single-dose studies can proceed regardless of results in genetic toxicity studies, and any positive results are included in the investigator's brochure and informed consent form.*
Merck Comment: It would be helpful for the guidance to include an additional sentence, such as, *For micro dosing studies, (e.g., PET tracer studies with a small fraction of pharmacological doses), single or multiple low doses can be given to healthy volunteers regardless of the genetic toxicology results.*

Lines 86-160: The Guidance states, *If a positive response is seen in one or more assays, sponsors should consider choosing from the following options.*
A. Weight-of-Evidence Approach (Lines 86-104)
Merck Comments:

- We agree that sponsors should assess the overall reproducibility of the response and its magnitude compared with historical controls, while examining the association with cytotoxicity. As one example of weight of evidence that would call into question biological significance, the Agency describes an increase seen in only one of the three arms of the chromosome aberration assay; it could be clarified in the Guidance that this would apply only when dealing with a very weak or equivocal increase in chromosome aberrations. The short- and long-treatment protocols in the *in vitro* chromosome aberration assay ask different questions and can inform about possible mechanisms. For example, a pulse (3-hour) treatment may lead to a positive result because the cells are able to progress to metaphase, whereas the continuous treatment

may cause sufficient cell cycle delay to prevent the appearance of aberrations at metaphase without a recovery period.

- We agree that a positive finding that is not corroborated by the matching exposure regimen of the mouse lymphoma assay could call into question the significance of a positive finding. However, emphasis on positive results in both assays does not necessarily increase the weight of evidence that this is a relevant result. Assessment of biological relevance by comparing results of the *in vitro* chromosome aberration and mouse lymphoma assays has limitations. As noted above, some of the mechanisms that lead to indirect/irrelevant positive results operate in both assay systems. This should be explained in the Guidance to avoid undue weight being given to genotoxic hazard should positive results be found in both the chromosome aberration and mouse lymphoma assays.

B. Mechanism of Action (Lines 106-118)

Lines 108-115: The Guidance states, ***Positive results are sometimes satisfactorily explained by knowledge of the mechanism of action. For example, it has been demonstrated that in vitro clastogenic effects can result from excessively high osmolarity or low pH. Positive responses elicited under such nonphysiologic exposure conditions are not relevant to human risk. In addition, certain genotoxic responses are thought to have thresholds below which a hazard does not exist. Agents that induce effects by indirect mechanisms, such as interference with metabolism of nucleotides and their precursors, damage to spindle proteins, or inhibition of topoisomerase, may have thresholds for genotoxic effects.***

Merck Comments:

- We agree; we would like to see an acknowledgement in the Guidance that the examples given do not comprise an exhaustive list. We suggest the inclusion of at least one other potential indirect mechanism, namely inhibition of DNA synthesis (Galloway, et al., Reference 1).

Lines 115-116: The Guidance states, ***In such cases, we recommend presenting direct evidence of the existence of a threshold that would not be attained during the proposed clinical exposure.***[This was all bolded; I corrected it, Sheila]

Merck Comments:

- Direct evidence of the existence of a threshold is not usually attainable, even for the examples given (e.g., interference with nucleotide metabolism, damage to spindle proteins or inhibition of topoisomerases). For example, it is difficult to construct a sufficiently detailed dose/time response curve to establish a threshold and it can be difficult to determine when there is a threshold of effect vs. a threshold of sensitivity of the assay. We submit that a more suitable statement in place of "presenting direct evidence of the existence of a threshold that would not be attained during the proposed clinical exposure" would be: "provide evidence of a threshold, a mechanism with a threshold, or an indirect mechanism not expected to operate under in vivo conditions".

- The Guidance should clarify that the statement, *Positive responses that are satisfactorily explained by an MOA may allow repeat-dose studies to proceed without additional studies*, refers to multiple dose trials in normal volunteers or in patients.

C. Additional Supportive Studies (Lines 122-160)

Merck Comments:

- In sections A and B, statements were made about the acceptability of proceeding to multiple-dose clinical trials in normal volunteers and in patients, when adequate weight of evidence or mechanism of action information was available. It would be appropriate to state in section C that when suitable evidence is available as outlined in sections A or B, or from additional studies on in vivo relevance (first part of section C), any early assessment of carcinogenic potential as outlined in paragraphs 3 and 4 of section C should not be required before progressing with multiple-dose clinical trials in normal volunteers and in patients.
- We request that the Agency clarify the reason for inclusion of the statements, *On occasion, results in in vitro studies demonstrate dose-responsive and reproducible positive responses,* and, *Results from the bone marrow cytogenetics studies are frequently negative, even for those compounds giving positive results in in vitro genetic toxicity assays*. In our experience, dose responsive, reproducible increases *in vitro* (e.g., in chromosome aberrations) can be seen with compounds that have threshold mechanisms, and with positive responses associated with cytotoxicity, etc. Is the intention to state that even when weight of evidence or attempts to determine mechanism of action do not explain an *in vitro* positive result, the *in vivo* assay may be negative?
- We request that the Agency specify the types of in vivo assays useful in clarifying *in vitro* positive results rather than specific methodologies. For example, "DNA strand break assays (including for example Comet and alkaline elution assays)" is preferable to limiting sponsors to "comet assays".
- The information cited on the SHE assay paragraph seems contradictory, in acknowledging the poor predictivity of the SHE assay for human risk (as also stated by Dr LeBoeuf in his publications on development of the assay [Reference 2]), yet stating that it maybe useful in making a WOE judgment. We disagree with the statement that, ... *.transformation assays measure endpoints more akin to the health effect of concern (cancer).* . . .." Human cells are extremely difficult to transform while rodent cells transform readily and the mechanism of transformation in unknown. Further details on the use of the SHE assay as a follow up assay are found in References 3 and 4. As noted above, we consider that as a general principle, a follow-up assay should be one that elucidates mechanism or adds understanding, and should not be an assay prone to false positive results. (The SHE assay was positive for 3 of 14 non-genotoxic, non rodent carcinogens in one study of Isfort et al, Reference 5). Those most experienced with the assay have cautioned that it is not predictive of human carcinogenic potential (Isfort and LeBoeuf, Reference 2). Thus rodent cell transformation *in vitro* might perhaps be useful in internal decisions by a sponsor on compound selection (as noted in ICH S1B), because it can be quite

predictive of genotoxic and non-genotoxic rodent carcinogens, and negative results in this assay have some value in lessening concern about carcinogenic potential.

However, it is not helpful in evaluating human safety and not an appropriate follow-up assay to genotoxicity testing, in deciding on progression to multiple dose clinical trials.

In conclusion, in addition to clarification of the points noted above, we strongly recommend that the proposed guidance be modified such that completion of the fourth test in the ICH standard battery is an option, and not a required first step in follow-up of a positive genetox test result.

We welcome the opportunity to comment on this draft Guidance and to meet with you to discuss our comments. Please feel free to contact me at (301) 941-1402.

Sincerely,

Brian Mayhew
U.S. Regulatory Policy

REFERENCES

1. Galloway SM, Miller JE, Armstrong, MJ, Bean CL, Skopek TR and Nichols WW (1998). DNA synthesis inhibition as an indirect mechanism of chromosome aberrations: comparison of DNA-reactive and non-DNA-reactive clastogens. Mutat Res. 400:169-186.

2. Isfort RJ and LeBoeuf RA (1996). Application of in vitro cell transformation assays to predict the carcinogenic potential of chemicals. Mutat Res. 365:161-173.

3. PhRMA/FDA Sponsored Workshop. Interpretation of positive genotoxicity data and follow-up testing. November 2003.

4. The PhRMA DruSafe Genetic Toxicology Work Group. DruSafe position of SHE cell assay. Society of Toxicology (SOT) Regulatory and Safety Evaluation Specialty Section-Newsletter. Spring 2004.

5. Isfort RJ, Kerkaert GA and LeBoeuf RA (1996). Comparison of the standard and reduced pH Syrian hamster embryo (SHE) cell in vitro transformation assays in predicting the carcinogenic potential of chemicals. Mutat Res. 356:11-63.